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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/776,190	01/24/97	JOSEL H	P564-7002

HM21/0528
NIKAIDO MARMELSTEIN MURRAY & ORAM
METROPOLITAN SQUARE
SUITE 330 G STREET LOBBY
655 FIFTEENTH STREET NW
WASHINGTON DC 20005-5701

EXAMINER	
RICIGLIANO,J	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 05/28/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/776,190	Applicant(s) Josel et al.
	Examiner Joseph W. Ricigliano Ph. D.	Group Art Unit 1648

☒ Responsive to communication(s) filed on *Mar 5, 1998*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *39-70* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *39-70* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Amendments Entered

1. Applicants' amendment and response, paper number 8, filed 3/5/98.

Claims 1-38 have been canceled and newly added claims 39-70 have been entered.

Claims 39-70 are pending in this application

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In view of applicants amendment, the rejection of claims 27-30 under 112 second paragraph is rendered moot.

Claim Rejections - 35 USC § 102

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 39, 41-44, 49, 50, 55, 56, 66, 69 and 70 originally presented as claims 1-6, 11, 12, 15, 16, 27, 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Bredehorst for reasons of record in paper number 7.

5. Claims 60 and 62 originally presented as 21 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith *et al* for reasons of record in paper number 14 4

Claim Rejections - 35 USC § 103

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 40 and 53 originally presented as claims 2 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst *et al* in view of Gadlow *et al* for reasons of record in paper number 14.

8. Claims 57-59 previously presented as claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst *et al* in view of Berzofsky *et al* for reasons of record in paper number 14.

9. Claims 66, and 68-70 previously presented as claims 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst *et al* in view of Smith *et al* for reasons of record in paper number 14.

10. Claims 61 originally presented as claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al* in view of Buchardt *et al* for reasons of record in paper number 14.

Response to Arguments

11. Rejection of claims over Datagupta *et al* under 35 U.S.C. 102 and 103

Applicants' arguments have been fully considered and have been found persuasive. Rejections, not repeated herein, in which Datagupta *et al* was the primary reference have been withdrawn.

12. Claims 39, 41-44, 49, 50, 55, 56, 66, 69 and 70 originally presented as claims 1-6, 11, 12, 15, 16, 27, 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Bredehorst for reasons of record in paper number 7.

Applicants' assertion that the Bredehorst reference does not anticipate the rejected claims because it did not teach derivatization during the synthesis. It is noted for the applicant that none of the claims rejected over Bredehorst alone required this in that the rejected claims are directed to the conjugates which are a product and not to the process. Since the products are the same the rejection is proper.

Applicants' assertion that the labeling groups are not placed at predetermined positions is not persuasive because the nitrophenyl and fluorescein groups are attached on the amino terminus and the free carboxyl group of the polymer respectively. Since the polymer (insulin) was of known sequence and structure, Bredehorst knew where the amino groups and the carboxyl groups were before using amino and carboxyl specific linking agents to attach the said molecules. Moreover, Bredehorst states explicitly where the sites of modification are, positions 4, 17 and 21 amino acids away from the hapten (the hapten is on amino acid 1: page 271 first column). Hence, Bredehorst *et al* does teach coupling to reactive side groups at predetermined positions. Therefore, Bredehorst *et al* anticipate claims 39, 41-44, 49, 50, 55, 56, 66, 69 and 70 of the instant application for the reasons above and for the reasons of record in paper number 7.

13. Claims 40 and 53 originally presented as claims 2 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst *et al* in view of Gadlow *et al* for reasons of record in paper number 7

14. Claims 57-59 previously presented as claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst *et al* in view of Berzofsky *et al* for reasons of record in paper number 7

Claims 66, and 68-70 previously presented as claims 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst *et al* in view of Smith *et al* for reasons of record in paper number 7.

Applicants have asserted the rejection of the above claims over a combination of Bredehorst in view of the Gadlow, Berzofsky or Smith references is flawed based upon flaws in the Brederhorst 102(b) reference. Applicants' attention is respectfully directed *supra* to the response to arguments with respect to the Bredehorst reference alone.

15. Claims 60 and 62 originally presented as 21 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith *et al* for reasons of record in paper number 7.

Applicants' arguments have been fully considered and found partially persuasive in that Smith does not disclose the use of multiple protective groups. Therefore, the rejection of claims 63-65 is withdrawn.

In that applicants have asserted that Smith *et al* discloses the conjugation of a dye to the 5' amino terminal monomer of the oligonucleotides of his invention, as was intended as was intended the syntheses recited by the applicant in their previous response, Smith et al in fact teach the modification of a predetermined position.

The assertion that reactions that do not go to completion are "statistical" and hence cannot be at predetermined positions is not persuasive. The extent of a reaction is not a

determinant the positions (which residues or monomers) which are being modified or if the sites were predetermined. Moreover, applicants' claims neither require any level of modification to be achieved in the synthetic process nor does the comprising language employed exclude subsequent purification.

It is clear therefore that Smith *et al* anticipate claims 60 and 62 for the reasons above and for the reasons of record in paper 7.

16. Claims 61 originally presented as claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al* in view of Buchardt *et al* for reasons of record in paper number 7.

Applicants have asserted the rejection of claim 22 is flawed based upon flaws in the Smith *et al* reference. Applicants' attention is respectfully directed *supra* to the response to arguments with respect to the Bredehorst reference alone.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

17. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

18. Claims 60-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brederhorst *et al* in view Green *et al*

19. See the teachings of Brederhorst as applied to claims 39, 41-44, 49, 50, 55, 56, 66, 69 and 70 under 35 U.S.C. 102(b) *supra*. Brederhorst does not teach the assembly of the peptides or the use of multiple protecting groups.

Greene *et al* teach the used of diverse amino and thiol protecting groups which can be applied and removed under a variety of conditions to achieve a desired synthetic goal, including acid labile and acid stable groups Chapters 2 and 6. Moreover, Greene *et al* teach "When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked" (page 1 first line of the text).

It would have been *prima facia* obvious at the time the invention was made to one of ordinary skill in the art to synthesize an amino acid based carrier (peptide) having 1-10 hapten molecules and 1-10 marker groups at predetermined positions on the carrier by synthesizing a peptide with protected positions, deprotecting and then reacting deprotected functionalities with haptens or markers with because Brederhorst *et al* teach a peptide with both hapten and marker groups at predetermined positions and Greene *et al* teach the use of a variety of protective groups that can be applied and removed under a variety of conditions to achieve the synthesis of a multifunctionalized molecule. One of ordinary skill in the art would have been motivated to utilize more than one protective group including acid labile and acid stabile amino protecting groups in order be able to selectively manipulate sites selectively in a multifunctional molecule while protecting the remaining sites as taught by Greene (page 1)

20. Claims 39, 41-48, 55 and 60-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchardt [WO 92/20702].

Buchardt teaches peptide nucleic acids, the monomers of which are both nucleotide analogs and amino acid analogs, formula III page 7 and the accompanying text. These PNA molecules can incorporate fluorophores (which reads on fluorescent labels) and antigen labels, which reads on a hapten, (page 14 lines 5-12 and page 20 lines 26-30 where haptens are specifically recited) or biotin (which reads on a solid phase binding group page 20 lines 26-30). Buchardt teaches the synthesis of PNAs (pages 24 to 27) and that the synthesis can place nucleobase monomers in any desired order "Following the coupling of the first amino acid the next stage of solid-phase synthesis is the systematic coupling of the desired PNA chain" (page 25 line 11-13). In that a PNA chain consists of nucleobases and the nucleobases comprise side chains (L-groups) which include: hydrogen, hydroxy, C1-4 alkanoyl, naturally occurring nucleobases aromatic moieties, DNA intercalators, nucleobase binding groups and reporter ligands" this reads on placing groups at predetermined positions (page 5 lines 4-10). In addition the side chains can be the side chains of naturally occurring amino acids, which includes tryptophan which reads on a fluorophore (see R7, page 7 line 7+ and page 8 line 35- page 9 line 1). Buchardt *et al* teach the formation of PNA DNA hybrids and PNA hybridization which reads on the limitations of claims 47, 48 and 66-68 (page 13 -14). Buchardt teaches the synthesis of PNAs (pages 24 to 27) and that the oligomers may be conjugated to low molecular weight effector ligands including reporter ligands (fluorescent, spin labels, radioactive, protein recognition ligands, for example biotin or haptens; page 20 lines 26-30) which reads on the

process of claims 55, 60 and 61. Buchardt teaches in reference to the incorporation of a detectable label "all those methods for labeling peptides, DNA and/or RNA which are presently known may in general terms be applied to PNA's" (page 14 lines 7-9) and the use of protecting groups in PNA synthesis page 23 line 8 through page 27) which reads on the limitation claim 62-65. Buchardt teaches the ability to immobilize a PNA and to displace a strand of the complex and the incorporation of antigen labels which reads on a competitive immunoassay which read on claims 69 and 70.

Buchardt does not teach a maximum length of 100 monomers for the conjugate.

It would have been *prima facia* obvious at the time the invention was made to one of ordinary skill in the art to produce a peptide nucleic acids conjugated to haptens solid phase binding groups and reporter labels because Buchardt teaches peptide nucleic acid conjugates including haptens solid phase binding groups (e.g., biotin) and reporter molecules. One of ordinary skill in the art would have been motivated to make conjugates less than 100 monomers long because Buchardt *et al* teach sequences from 5-60 base pairs (monomers) long are especially useful (page 13 lines 14-26). One of ordinary skill in the art would have expected to be able to synthesize conjugates of this length because Buchardt had taught extensively on their synthesis.

21. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano Ph. D. whose telephone number is (703) 308-9346.

The examiner can normally be reached on Monday through Thursday from 7:30 A.M. to 5:00 P.M. and alternate Fridays from 7:30 A.M. to 5:00 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald Adams, can be reached at (703) 308-0570.

Joseph W. Rieglano Ph. D.

DONALD E. ADAMS
SUPERVISORY PATENT EXAMINER